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THE PREPARATION OF SOME MERCAPTO MONOSACCHARIDES

A DISSERTATION

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by

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ABSTRACT

Methyl 4,6-O-benzylidene-2-benzylthio-2-deoxy-α-D-altropyranoside and methyl 4,6-O-benzylidene-3-benzylthio-3-deoxy-α-D-altropyranoside have been prepared by the reaction of sodium benzylmercaptide on methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside and methyl 2,3-anhydro-4,6-O-benzylidene-α-D-mannopyranoside, respectively.

These two thioethers were successfully completely reduced by sodium in liquid ammonia to methyl 2-deoxy-2-mercapto-α-D-altropyranoside and methyl 3-deoxy-3-mercapto-α-D-altropyranoside. In both cases bibenzyl was found as a by-product of this reduction. An attempted selective reduction of the benzylthio group, using a limited amount of sodium in liquid ammonia, was unsuccessful.

Treatment of 1,2:5,6-di-O-isopropylidene-3-O-tosyl-α-D-glucofuranose with sodium benzylmercaptide yielded only detosylated diacetone glucose.

ACKNOWLEDGEMENTS

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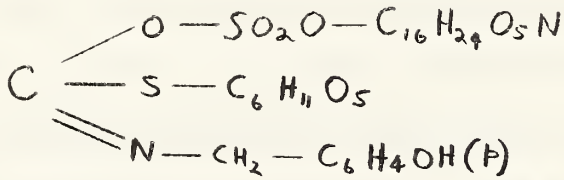
INTRODUCTION

The synthesis of mercapto monosaccharides was undertaken primarily to provide compounds which would permit the study of the formation and cleavage of mixed acetals. In addition, the properties and reactions of monosaccharides in which at least one hydroxyl has been replaced by a mercapto group might be significantly different to warrant further study. Furthermore, in view of the importance of sulphur compounds in biological systems, the mercapto monosaccharides might well exhibit some interesting physiological effects.

While in the present instance the work was done on hexoses - because of the ready availability of the starting material, glucose - the method should be equally applicable to the pentoses.

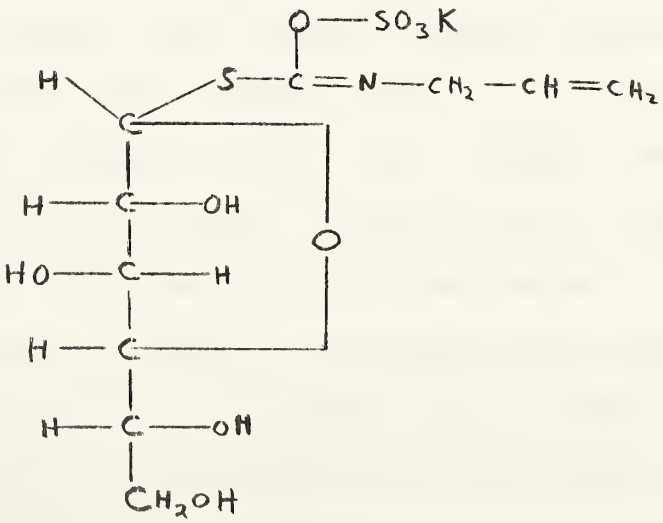
LITERATURE SURVEY

The first known example of a sulphur-containing monosaccharide was reported in 1831 by Robiquet and Boutron-Charland (1). These two workers isolated from mustard seed a substance, sinalbin, which proved to be a thioglycoside liberating a reducing sugar on acid hydrolysis.



Sinalbin

Shortly afterwards, Boutron and Robiquet (2) isolated another substance, sinigrin, again from mustard seed and this also proved to be a thioglycoside of the following structure.



Sinigrin

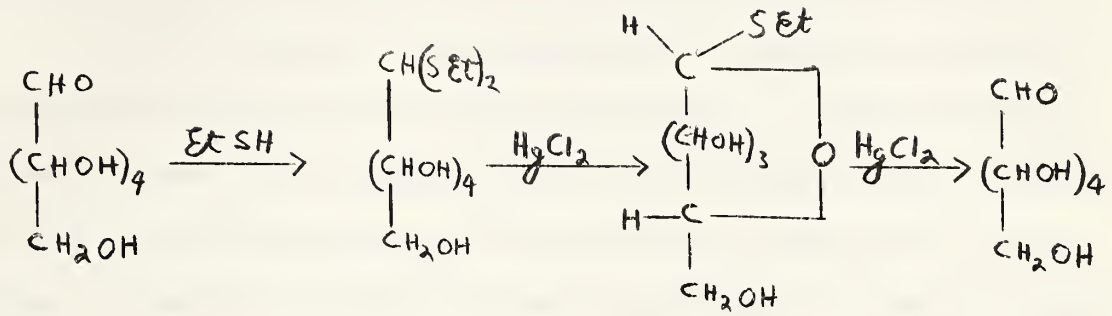
The furanose ring structure for the glycoside was adopted by the early workers in conformity with the general practice of the time, but its existence was not confirmed.

Hydrolysis with the enzyme myrosin yielded D-glucose. However, when Schneider and Wrede (3) used potassium methoxide as the hydrolizing agent, l-thioglucose was isolated.

Credit for the first synthetic thioglycoside is due to Fischer and Delbruck (4) who, in 1909, synthesized a phenyl-thio D-glucoside by treating acetobromo-D-glucose with sodium thiophenoxide. From the method of synthesis, via S_N2 attack, the product is evidently of the β configuration and it is interesting to note that, unlike all the natural thioglycosides, it is not hydrolizable by the enzyme myrosin. This enzyme may, therefore, be assumed to be either an α-thiopyranosidase or a thiofuranosidase.

There are several other reported methods for the preparation of thioglycosides but probably the best known was developed by Schneider and Sepp in 1916 (5). Fischer had shown earlier (6) that the reducing sugars resemble simple aldehydes in that they will react with two moles of a mercaptan to yield a mercaptal or thioacetal, a reaction which has since been widely used in the preparation of aldehydo or keto open-chain derivatives. It remained for Schneider and Sepp to make the important observation that in the presence of aqueous mercuric chloride, these mercaptals would successively split off first

one and then both alkylthio groups according to the following scheme.



Invaluable as this reaction has proved to be in synthetic work, it does not permit the synthesis of free 1-thio-sugars.

As was mentioned above, free 1-thioglucose has been liberated from natural thioglucosides chemically, but to Wrede (7) goes the credit for first synthesizing it. In 1919 he reported that the reaction of acetobromo-glucose with potassium disulphide gave the diglucosyl disulphide. Three years later (8), he described the reduction of the disulphide with zinc and acetic acid followed by the removal of the acetyl groups with ammoniacal methanol and thus prepared the first synthetic 1-thio-D-glucose.

Wrede found the properties of 1-thioglucose to be similar to those of normal monosaccharides and while the sweet taste of glucose was absent, it resembled this substance in solubility and its ability to reduce Fehling's solution in the cold. Another characteristic common to both glucose and 1-

thioglucose is that of mutarotation, a property which has been investigated in the latter compound by Schneider et al (9).

Over twenty years elapsed before evidence for the ring size of 1-thioglucose was published. In 1943 Richtmyer, Carr and Hudson (10) prepared the disulphide by Wrede's method but used aluminum amalgam for reduction to obtain the 1-thioglucose. When the thioglucose was subjected to further catalytic reduction, it was found to yield polygalitol tetra-acetate, a compound known to have a 1,5-anhydro ring. It, therefore, seems probable that 1-thioglucose exists preferentially in the pyranose ring form.

A recent approach to the synthesis of 1-thiosugars has been reported by Prey and Grundschober (11). These two workers treated 1,2-anhydro-D-glucopyranose with hydrogen sulphide for 12 hours at 70°C under a pressure of 10 atmospheres and were able to isolate from the reaction mixture both α- and β-1-thio-D-glucopyranose. Their work was based on the earlier observations of Ohle and his co-workers (12) that crystalline 6-deoxy-1,2-O-isopropylidene-6-mercapto-α-D-glucofuranose could be synthesized quantitatively by the reaction of hydrogen sulphide on 5,6-anhydro-1,2-O-isopropylidene-α-D-glucofuranose in a suspension of barium hydroxide at 0°C. These earlier workers were, however, unable to crystallize the free 6-deoxy-6-mercapto-α-D-glucofuranose on removal of the isopropylidene group.

So far in the discussion of thiosugars, the sulphur

atom has always been attached to the anomeric carbon, and while examples of this type are the most frequently encountered in the literature, they are by no means the only ones to be found.

The second most common structure is that in which the sulphur atom is incorporated in the terminal, primary group, i.e. on C_6 of a hexose or C_5 of a pentose. The only known naturally-occurring thiosugar of this category is the reputed "5-deoxy-5-methylthio ribose" which is present in yeast as its adenine glycoside. Mandel and Dunham (13) were the first to isolate this nucleoside but considered the carbohydrate moiety to be a sulphur-free hexose. The carbon and hydrogen values found for this sugar along with the carbon, hydrogen and nitrogen percentages of its osazone, substantiated their belief in the hexose structure of this glycoside. However, since the molecular weight of sulphur is twice that of oxygen, the proportion in which these elements are present is also that to be expected from a methylthio-pentose. Raymond (14), synthesized 5-deoxy-5-methylthioxylose and found its osazone to be different from that of the naturally-occurring compound which he prepared for purposes of comparison. Wendt (15) concludes from lead tetraacetate oxidation studies that the sulphur cannot be on C_3, but the final structure of this naturally-occurring thiosugar has not yet been proved conclusively.

The first successful synthesis of a carbohydrate containing a sulphur atom attached to the primary carbon was achieved by Wrede (16) in 1921. He treated methyl-6-bromo-6-

deoxy-β-D-glucopyranoside-2,3,4-triacetate with potassium hydrogen sulphide and on subsequent deacetylation and hydrolysis, obtained a disaccharide of two glucose molecules joined through their C_6 atoms by sulphur.

A more recent synthesis of a monosaccharide with sulphur attached to the primary carbon atom has been achieved by Baker (17). He treated 1,2:3,4-di-O-isopropylidene-6-O-tosyl-α-D-galactopyranose with sodium ethylmercaptide and was able to isolate 6-deoxy-6-ethylthio-α-D-galactopyranose.

The above review has been concerned solely with monosaccharides containing a sulphur atom attached to either the anomeric carbon or the terminal primary carbon. However, in 1932, Brigl and Schinle (18) reported the synthesis of the first monosaccharide with an alkylthio group attached to a non-terminal carbon. They found that treatment of 3,4,5,6-tetra-O-benzoyl-aldehydo-D-glucose with ethyl mercaptan and hydrochloric acid gave rise initially to the expected mercaptal benzoate. However, on extending the reaction time, the C_2 hydroxyl was replaced by an ethylthio group.

The same compound was again isolated by treating 1,2,3,5,6-penta-O-benzoyl-D-glucofuranose and 2,3,4,6-tetra-O-benzoyl-D-glucopyranose with ethyl mercaptan and hydrochloric acid. They suggest that the ring is opened with the addition of two moles of ethyl mercaptan on C_1 followed by a migration

of the benzoyl group from C_2 to C_4 or C_5. Mercuric chloride removed the thioacetal groups and the position of the remaining thioether was demonstrated by preparing a sulphur-containing phenylhydrazone and a sulphur-free glucosazone.

When 3,5,6-tri-O-benzoyl-1,2-O-isopropylidene-α-D-glucofuranose was subjected to the same conditions, the isopropylidene residue was removed and a substance containing four ethylthio groups was isolated. The authors postulate this to be the thioacetal with the additional two ethylthio groups on positions 2 and 4.

A similar reaction was performed by Wolfram and Thompson (19) using zinc chloride as a catalyst in place of hydrochloric acid. They found that two acetyl groups of glucoheptulose hexaacetate were replaced by ethylthio-units to give a crystalline ethylthioglucoheptuloside tetraacetate containing a second ethylthio group on an unspecified position in the chain.

More recently, a novel approach to deoxy sugars (20, 21), involved the synthesis of methyl 4,6-O-benzylidene-2-deoxy-2-methylthio-α-D-altropyranoside and methyl 4,6-O-benzylidene-3-deoxy-3-methylthio-α-D-altropyranoside from the corresponding 2,3-anhydroalloside and 2,3-anhydro-mannoside derivatives. By subsequent desulphurization with Raney nickel, there was produced both 2- and 3-deoxyaltrosides.

Similar reactions have been performed in the pentose series by Baker (22). In an attempt to synthesize 2-deoxy-β-

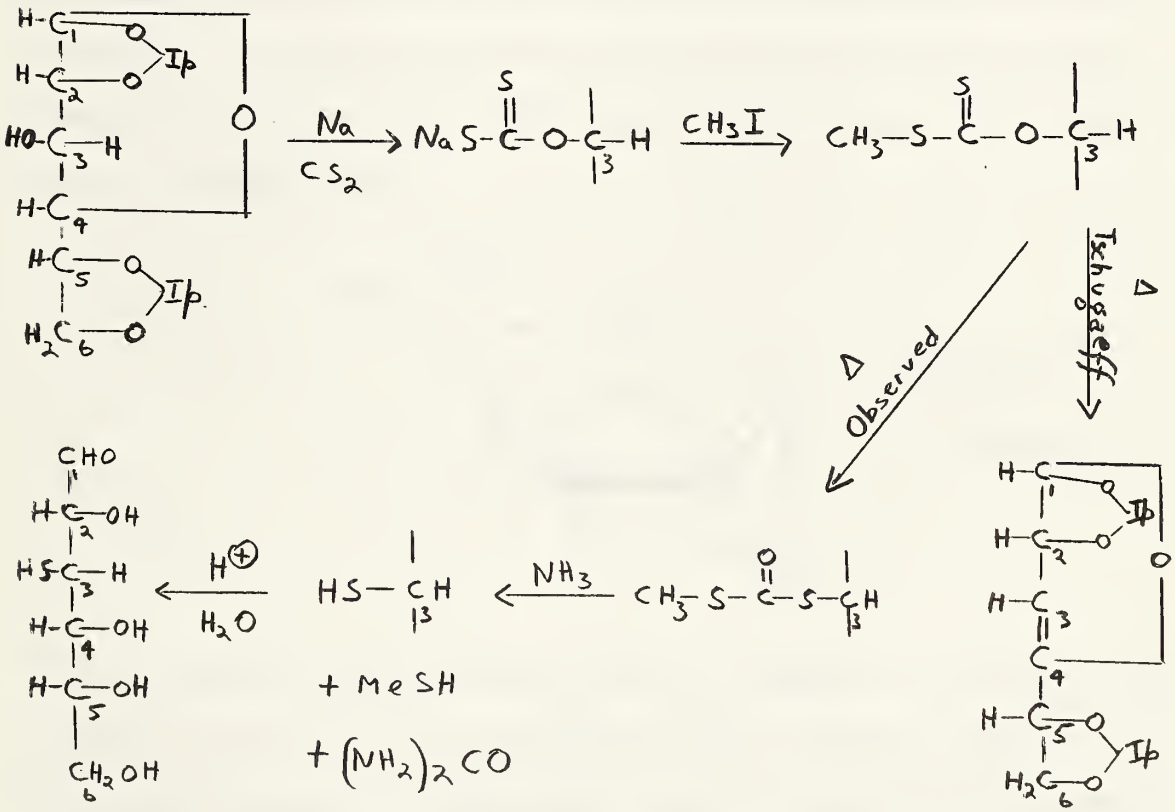
D-ribofuranose, he treated methyl 2,3-anhydro-β-D-ribofuranoside with excess sodium ethylmercaptide and obtained an essentially quantitative yield of the 3-ethylthio compound. On treatment with p-toluenesulphonyl chloride and subsequent acetolysis with sodium acetate in refluxing Cellosolve, the 3-ethylthio group migrated via an episulphonium ion to give the isomeric 2-ethylthio compound. Desulphurization with Raney nickel yielded the desired 2-deoxy sugar.

The interest in preparing these carbohydrate thioethers just discussed arose from a desire to synthesize deoxy sugars. However, this approach has now been superseded by a method developed by Prins (23) involving direct reduction of the epoxides with lithium aluminum hydride. Thus, on such a reduction, methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside yielded methyl 4,6-O-benzylidene-2-deoxy-α-D-altropyranoside, while methyl 4,6-O-benzylidene-3-deoxy-α-D-altropyranoside was obtained from methyl 2,3-anhydro-4,6-O-benzylidene-α-D-mannopyranoside.

Apart from the previously mentioned 1-thiosugars and the 6-deoxy-1,2-O-isopropylidene-6-mercapto-α-D-glucofuranose of Ohle et al (12), the only other example of the synthesis of a monosaccharide containing a free mercapto group - as distinct from a thioether - was that reported in 1927 by Freudenberg and Wolf (24). Although it is not the purpose of this literature survey to discuss previous work in detail, since no one

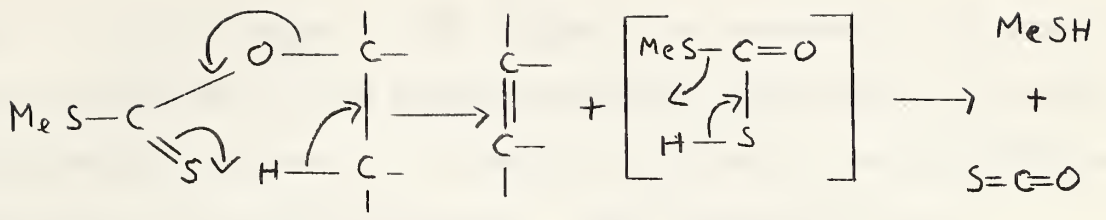
appears to have re-examined Freudenberg's work in the light of more recent knowledge, it might be of interest to digress slightly at this point.

In an attempt to prepare an unsaturated sugar by way of the Tschugaeff Reaction (25), Freudenberg and Wolf prepared the xanthate of diacetone glucose by treating it with sodium and carbon disulphide. The scheme of reactions is indicated below.

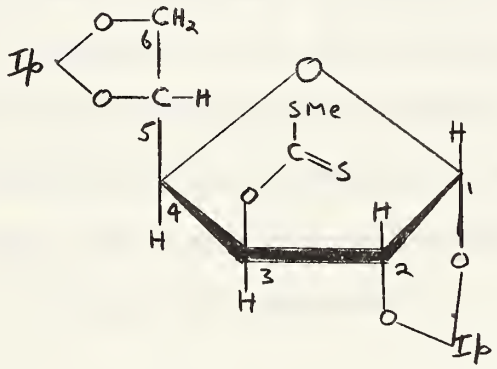


Ip = Isopropylidene.

Normally in the Tschugaeff Reaction, heating the xanthate results in unsaturation occurring via a cyclic intermediate which depends on the presence of a hydrogen atom cis to the xanthate group (26).



From the structural representation of the diacetone glucose xanthate above, it appears that both the C_2 and C_4 hydrogens are suitably orientated for dehydration to occur. However, if the xanthate is written more correctly in the Haworth structure (27) which was not published until after this work of Freudenberg,



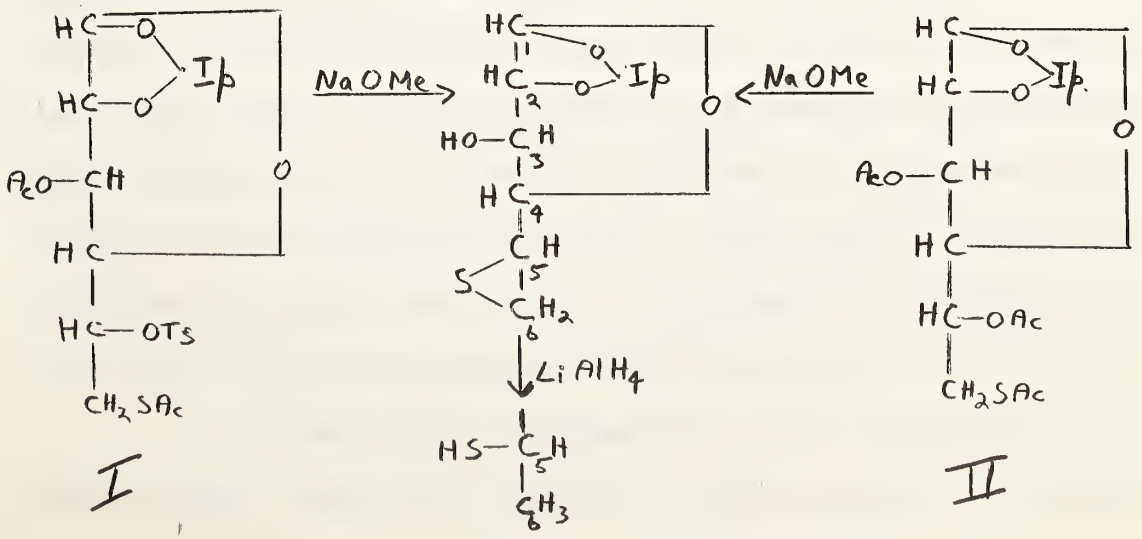
Haworth Structure.

it is readily seen that only the C_2 hydrogen is in the required relationship cis to the xanthate group. Thus, even had the Tschugaeff reaction proceeded normally, the 2,3-unsaturated sugar would have been produced rather than Freudenberg's expected 3,4-unsaturated isomer.

In fact it was found that rather than causing unsaturation, heating the xanthate appeared to bring about a rearrange-

ment of the R·CO·S_2Me to R·S·CO·SMe. On treatment with ammonia this decomposed to give methyl mercaptan, urea and a compound tentatively described as "3-deoxy-1,2:5,6-di-O-isopropylidine-3-mercapto-α-D-glucofuranoside". This sugar would not crystallize nor could it be induced to do so after removal of the isopropylidene groups. The configuration at C_3 remains undetermined. Diacetone galactose and diacetone mannose were treated in a similar manner but neither could be induced to undergo a Tschugaeff Reaction nor to react in a manner analogous to that of glucose.

In a paper published in 1960, Owen (28) described two methods for the preparation of the mercapto sugar, 5,6-dideoxy-1,2-O-isopropylidene-5-mercapto-α-L-idose. Both approaches involve the intermediate 5,6-dideoxy-5,6-epithio-1,2-O-isopropylidene-α-L-idose which appears to be the first known episulphide in carbohydrate chemistry.



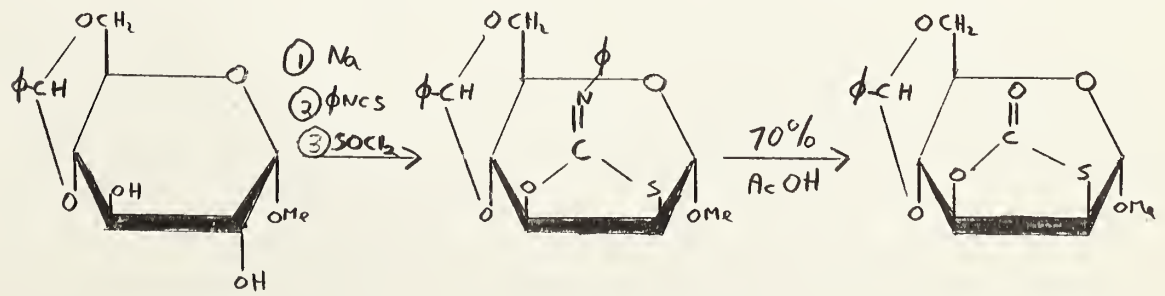
When prepared from II, the yield was only 10%. However, when I was the precursor, the yield was increased to 73% which is understandable as the tosyloxy group is known to be a better leaving group than is the acetoxy.

In a following paper (29), the same author describes the preparation and reductions of the trithiocarbonates of some sugar alcohols. The first carbohydrate trithiocarbonate was prepared by Wiggins (30) in 1951 by treating 5,6-anhydro-1,2-O-isopropylidene-α-D-glucofuranose with carbon disulphide which yielded crystalline 5,6-dideoxy-1,2-O-isopropylidene-5,6-(thiocarbonyldithio)-α-D-glucofuranose. Wiggins' main interest, however, was in the preparation of deoxy-sugars and accordingly he reduced the trithiocarbonate with Raney nickel to 5,6-dideoxy-1,2-O-isopropylidene-α-D-glucofuranose. In a similar manner, the analogous derivatives of sorbitol and mannitol were prepared. While Owen made no specific mention of the reduction of carbohydrate trithiocarbonates, the corresponding lithium aluminum hydride reductions of the related hexitol trithiocarbonates leave little doubt that this is an excellent route to the synthesis of dimercapto monosaccharides. Thus 5,6-dideoxy-1,3:2,4-di-O-ethylidene-5,6-dimercapto-L-iditol was conveniently prepared in 88% yield by the lithium aluminum hydride reduction of 5,6-dideoxy-1,3:2,4-di-O-ethylidene-5,6-(thiocarbonyldithio)-L-iditol.

Two other recent approaches to the synthesis of mercapto sugars have been reported by Baker et al in a series of

papers on potential anticarcinogenic compounds.

Ribose is a most vital naturally occurring sugar and replacement of one of its hydroxyls by a mercapto group would very probably confer upon it some interesting physiological properties. Since the C_2 and C_3 hydroxyl groups in the parent ribose are in a cis configuration, it would seem desirable to introduce the mercapto group cis to one of these hydroxyl units. A one step synthesis by epoxide ring opening is obviously inapplicable in this case since the attacking nucleophile must enter trans to the vicinal hydroxyl. Baker (31), therefore, attempted to achieve a conversion of trans to cis configuration by way of neighbouring group interaction and, as a model chose methyl 4,6-O-benzylidene-α-D-glucopyranoside. This was treated first with phenyl isothiocyanate and reaction of the resulting 3-thiourethan with thionyl chloride caused cyclization to the anil. Treatment with 70% acetic acid yielded another oil with an infrared carbonyl absorption at 1742 cm^{-1}, presumably from the thiolcarbonate.



However, the acid conditions employed removed some of the benzylidene group and gave rise to unstable mixtures. Accordingly, in a following paper (32) he reverted to the simpler trans-1,2-cyclopentane-diol system which on treatment in the above manner was successfully converted to the cis mercapto alcohol.

A more recent paper from the same laboratory (33) describes the preparation of the hitherto unknown episulphide, 4,6-O-benzylidene-2,3-dideoxy-2,3-epithio-α-D-allopyranoside by treating the oxygen analogue of the mannoside with ammonium thiocyanate, mesylating the resulting hydroxyl group and finally treating with aqueous sodium hydroxide. Presumably the lithium aluminum hydride reduction of this compound would yield methyl 4,6-O-benzylidene-2,3-dideoxy-3-mercapto-α-D-altropyranoside, though the authors make no mention of this.

RESULTS AND DISCUSSION

From the preceding Literature Survey, it can be seen that while there have been a few references to mercapto sugars throughout the literature from early days, no one to date has proposed a simple general method for their preparation. Previous work in this laboratory on the preparation of mercaptoindoles (34) by synthesizing first the benzylthio ether followed by a reductive cleavage with sodium in liquid ammonia, seemed to be compatible with carbohydrate chemistry and, in fact, has proved to be a convenient route to the synthesis of mercapto sugars.

As mentioned previously, one method of introduction of a thioether into a monosaccharide had been pioneered by Jeanloz, Prins and Reichstein (20,21) who attacked a 2,3-epoxide ring with sodium methylmercaptide and obtained the required thioether in good yield. Substitution of benzyl for methyl mercaptan and subsequent sodium in liquid ammonia reduction therefore seemed a promising method for obtaining mercapto monosaccharides. It was decided to attempt to prepare by this method both the 2- and 3-mercapto-altrosides from the 2,3-anhydro-alloside and 2,3-anhydromannoside, respectively. The reason for the specific opening of these rings will be discussed later.

The value of epoxides in the preparation of rare sugars from easily accessible ones is well realized and a

recent review by Newth (35) is devoted entirely to them. Epoxides are almost invariably prepared by the hydrolysis of suitable sugar sulphonic esters - another important class of carbohydrate derivatives also the subject of an excellent comprehensive review (36). Though these sulphonyl compounds may be synthesized in several ways, the one finding most general use involves esterification of the alcohol with a sulphonyl chloride in the presence of a base - frequently pyridine. This was the method chosen for the present investigation. The reaction of p-toluenesulphonyl chloride with hydroxyl-containing compounds will be referred to as "tosylation" in accordance with customary usage.

Since a 2,3-epoxide was desired, it was essential to block other reaction sites prior to commencing tosylation. The anomeric carbon was first shielded by conventional glycoside formation with methanol (37), a reaction which was found to proceed very smoothly and in yields in accordance with those reported.

The 4 and 6 positions were now protected by preparing the benzylidene derivative from benzaldehyde in the presence of zinc chloride. The general basis for this preparation was the work of Freudenberg, Toepffer and Anderson (38), but the three-hour reaction time recommended by them was deemed insufficient as a considerable quantity of unreacted solid material remained after three hours. Accordingly, the reaction was

allowed to proceed 24 hours as was advocated for the preparation of 4,6-O-benzylidene-α-D-glucose (39). After this increased reaction time, all solid particles were found to have disappeared. The benzaldehyde used to prepare the acetal was distilled immediately before use since contaminating benzoic acid lowered the yield of product. Distillation of the benzaldehyde under an atomosphere of nitrogen gave no improvement and hence was considered unnecessary. Thorough washing of the product with pentane was found to be essential prior to recyrstallization from water in order to remove excess benzaldehyde occluded in the crystals.

The above two reactions left only positions 2 and 3 available for tosylation.

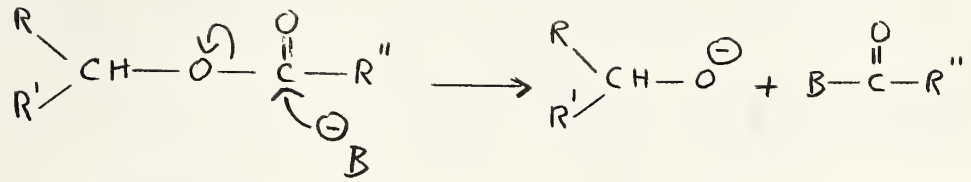
Initial interest in carbohydrate sulphonic esters centred around their use as crystalline derivatives for identification purposes, as many of them crystallize with comparative ease. All literature methods of ditosylation of methyl 4,6-O-benzylidene-α—D-glucopyranoside refer back to the original publication of Ohle and Spencker (40) who employed a 50% excess of tosyl chloride and a reaction time of four days at 30°C. However, their method of isolating the products by removal of the pyridine by distillation was later improved by Richtmyer and Hudson (41) who poured the reaction mixture into ice cold water whereupon the tosylated sugar solidified.

In the present investigation, a commercial grade of tosyl chloride available in this laboratory was employed but

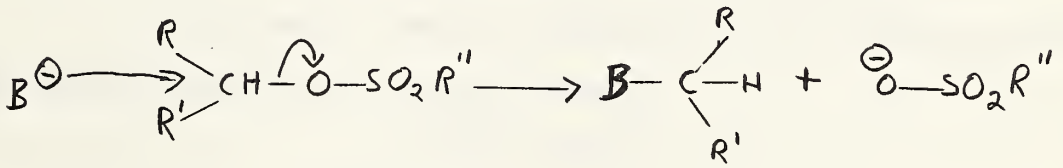
required preliminary purification for satisfactory results. A 10% excess of this reagent was found to be sufficient and, as complete tosylation was desired, the reaction time was extended to a week at room temperature. This increased reaction time was preferred since Richtmyer and Hudson once found that some monotosyl derivative was formed as a minor contaminant after four days (41). As a further modification, at the end of the reaction time, water was added to the mixture, a few mls. at a time with swirling, to ensure complete hydrolysis of the excess tosyl chloride which is otherwise only slowly destroyed on being poured into the ice-cold water (36).

Monotosylation was achieved by Bolliger and Prins' method (42) involving an overnight treatment with tosyl chloride followed by isolation as above. The monotosyl ester was obtained as a solid but recrystallization was difficult, involving large volumes of solvent and giving only poor yields. A small quantity was purified by recrystallization from methanol for identification purposes while the remainder was found to detosylate quite satisfactorily in the crude state.

It is well known that a fundamental difference exists in the hydrolysis of carboxylic and sulphonic esters. Whereas the former split by O-acyl fission,

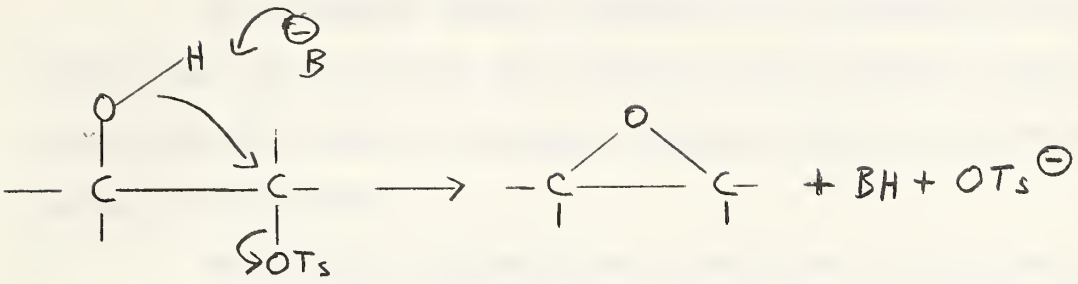


the latter undergo O-alkyl cleavage.



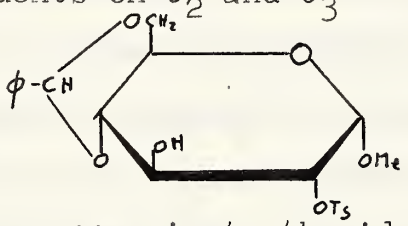
This second scheme involving cleavage of the carbon-oxygen bond explains the epoxide formation on hydrolysis of tosylated carbohydrates with appropriately oriented contiguous groups.

If the vicinal groups are cis, as in methyl 2,3,6-tri-O-acetyl-4-O-methanesulphonyl-β-D-galactopyranoside, the sugar remains mesylated and only deacetylation occurs on treatment with sodium methoxide (43). However, should an adjacent hydroxyl group be in the favoured orientation, trans to the tosyloxy group, it can displace the sulphonyloxy group and form an epoxide by an intramolecular S_N2 process.



This illustrates the formation, in the present series of reactions, of the 2,3-anhydro-mannoside from the methyl 4,6-O-benzylidene-2-O-tosyl-α-D-glucopyranoside.

The simple Haworth structure of the monosaccharide shows the substituents on C_2 and C_3



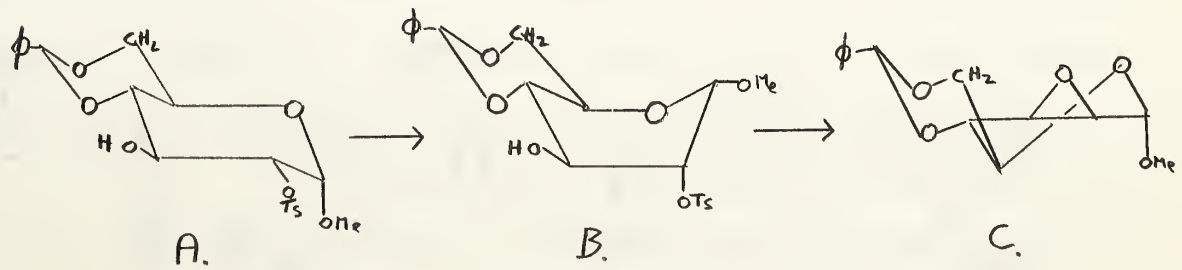
in glucopyranose to approximate the ideal trans diaxial configuration for elimination of the tosyl group as illustrated above. However, it is now recognized (44) that useful as the Haworth representation is, it cannot account for the many apparently anomalous reactions to be found in sugar chemistry. In fact, the carbohydrates must be represented as being conformationally similar to the boat and chair "flip" forms of cyclohexane.

There is little energy required for the interconversion of these flip forms and in eliminations from monocyclic systems, the necessary conformational change to bring the reacting groups into the trans diaxial arrangement is usually fairly readily achieved.

The present system, however, is a rigid one, for the benzylidene group keeps the pyranose ring fixed in the C_1 conformation (44) with all groups, except that on the anomeric carbon, equatorial.

That such conformation effects are a very real factor in elimination reactions has been vividly illustrated by Barton and Rosenfelder (45) who studied two steroids, identical but for the conformation of two bromine atoms. In one case these were held rigidly diaxial, in the second, diequatorial. Debromination by iodide ion occurred in the former compound over the course of a few days whereas the latter showed no indication of reaction even after six months.

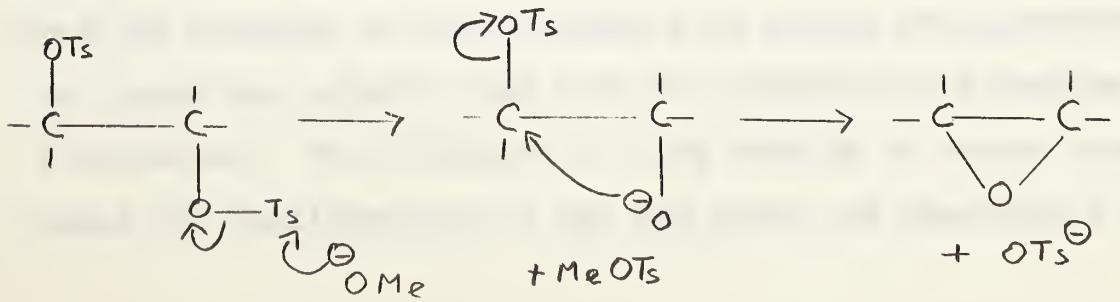
In spite of this, detosylation of the 2-O-tosyl sugar occurs with comparative ease, a fact which suggests some structural modification prior to elimination. To account for this, Newth (46) postulated a downward movement of C_2 to the boat form (i.e. A→B) thus approximating a trans diaxial state for the groups on C_2 and C_3 without affecting the point of ring fusion.



It is now a simple matter for elimination of the tosyloxy group to occur giving rise to the anhydro mannoside which exists in the half chair form (C) analogous to the structure of cyclohexene oxide.

The above considerations explain the formation of the anhydro-mannoside from the 2-O-tosyl compound but some modifications are necessary to account for the anhydro-alloside formation from the 2,3-di-O-tosyl ester.

As was mentioned earlier, the characteristic of sulphonic acid ester hydrolysis which makes possible epoxide formation is its O-alkyl fission. However, it is obvious that in the case of a di-O-sulphonyl compound, one group must split O-acyl. Cope and Shen (47) in a paper on the tosyl esters of dianhydro hexitols, have named this characteristic reaction S_N2S. The more accessible group is of course the one most readily attacked by the base and hence the first to leave via acyl oxygen cleavage and its departure is facilitated by the inductive effect of the second tosyloxy group as illustrated below.



The possibility of a concerted mechanism suggests itself but is not in keeping with experimental data reported by Honeyman and Morgan (48). They found that while extended treatment of the ditosylate with sodium methoxide gave the anhydro alloside, a shorter reaction time yielded some methyl 4,6-O-benzylidene-3-O-tosyl-α-D-glucopyranoside. This not only substantiates the above two-stage mechanism but also illustrates the greater accessibility of the 2-O-tosyl group.

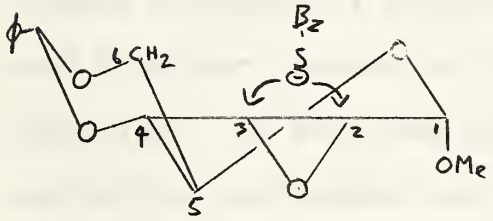
In practice, in this laboratory, solvolysis of the ditosylated sugar was achieved by Richtmyer and Hudsons' method (41) involving treatment of a chloroform solution of the diester with sodium methoxide at 0°C. This procedure gave a nearly quantitative yield of the anhydro alloside. However, in place of the chloroform/ether mixture used by these two workers as the solvent for crystallization, the aqueous acetone mixture of Robertson and Griffith (49) was found to be more satisfactory.

The anhydro-mannoside was obtained from the crude methyl 4,6-O-benzylidene-2-O-tosyl-α-D-glucopyranoside after a four-hour reflux period with sodium methoxide (49).

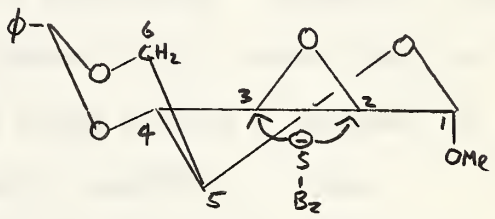
The next step in the synthesis of the thioaltrosides was the reaction of the epoxides with sodium benzylmercaptide to cleave the anhydro ring with the concomitant formation of a thioether. The direction of ring opening of course determines the configuration of the new sugar and therefore it

seems worthwhile at this stage to consider some of the salient points of this epoxide cleavage.

The attacking nucleophile must approach the pyranose ring from the opposite side from the epoxide oxygen, i.e. from above in the case of the alloside and from below in the mannoside isomer. In either case, two possible sites of attack at C_2 and C_3 are available to the nucleophile.



Anhydro-alloside

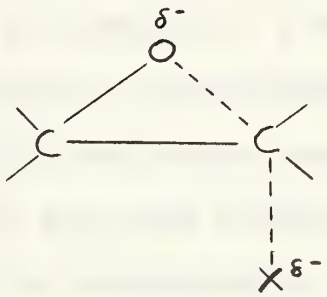


Anhydro-mannoside

It soon becomes apparent on a survey of the literature on ring-opening of epoxy sugars that one isomer is produced in large excess over - if not to the exclusion of - the other. Thirty-five of the forty reactions of sugar epoxides, stabilized by the presence of a second ring, reviewed by Overend and Vaughan (50) open to give diaxial products. Of the five exceptions which yield diequatorial isomers, two are acid catalyzed, and presumably the stabilizing benzylidene ring is removed by hydrolysis prior to epoxide ring opening. Two are heterogeneous hydrogenations which may well differ mechanistically. The fifth is quite unique as it reports diaxial opening of methyl

2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside with ethyl magnesium bromide (51) but diequatorial with methyl magnesium bromide (52). No explanation has yet been proposed to explain this anomaly.

Peat in his review on anhydro sugars (53) offers no explanation for the preponderance of one isomer over the other. This is understandable since Reeves' (44) work on the conformational analysis of sugars was not yet published. However, Furst and Plattner, quoted by Parker and Isaacs (54), state that in steroids, the scission of an epoxide ring yields a product in which the new groups are in the diaxial position. Bose, Chaudhuri and Bhattacharyya (55) were the first to apply the same reasoning to the carbohydrates, and postulate that in the transition state,



with the C-O bond partially cleaved and the C-X bond partially formed, both the attacking nucleophile X and the epoxide oxygen have associated with them fractional negative charges. In the chair conformation, which must be formed after cleavage, the distance between the diaxial substituents is greater than

that between diequatorial groups, and they suggest that the repulsion between the like charges will enhance the probability of the diaxial transition state being formed.

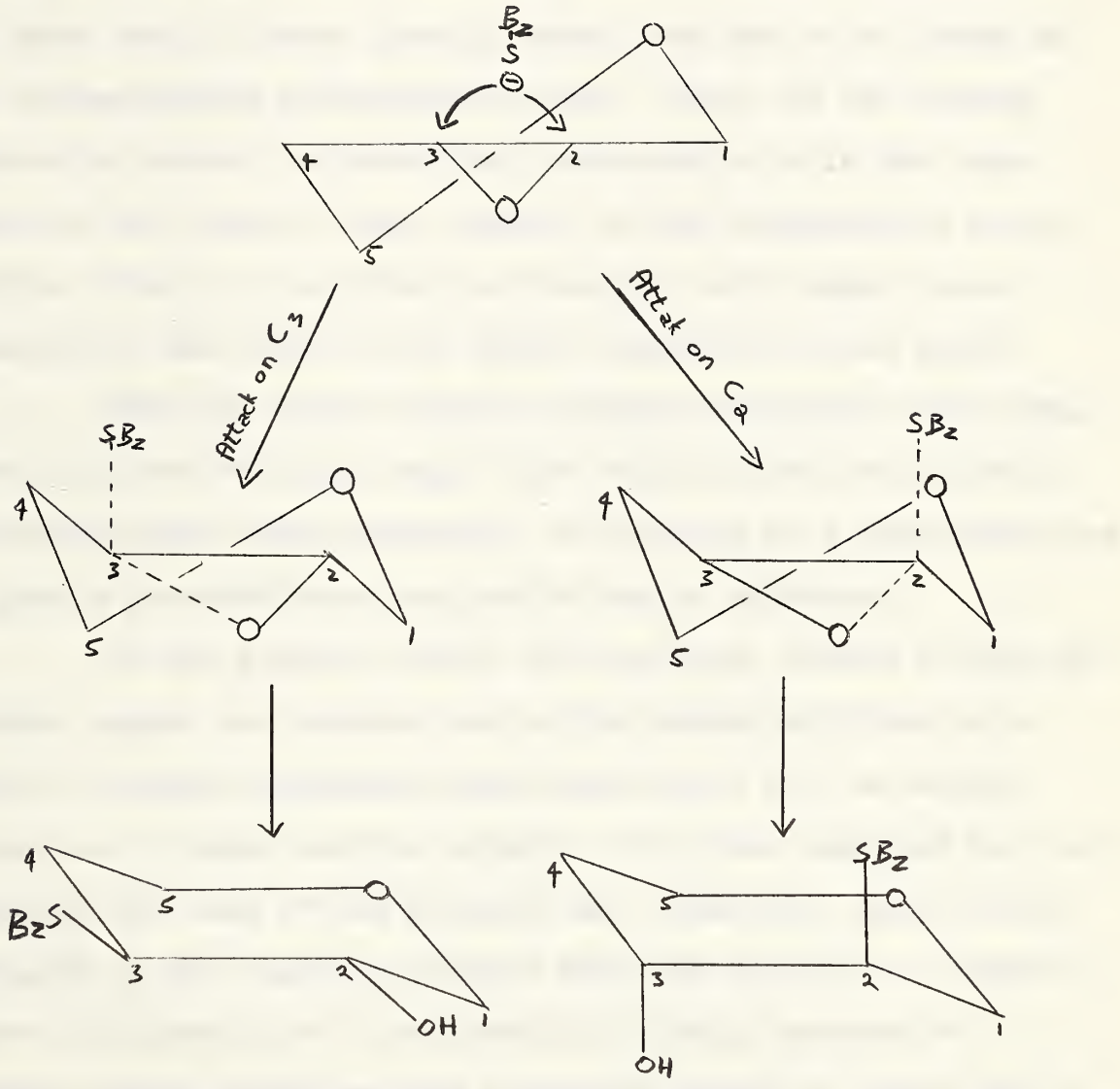
However, as noted by Cookson (56), if this were indeed the determining factor, scission by acids - in which the oxygen is presumably associated with a proton - should yield preferentially diequatorial products, which is not in accordance with cases reported in the literature. He, therefore, suggests that an explanation be sought from geometric, rather than electrostatic considerations and Parker and Isaacs have restated this viewpoint in their review on the mechanism of epoxide reactions (54).

It should be stressed again at this point that the anhydro sugar adopts the half-chair conformation of cyclohexene oxide, as the fusion of a three-membered ring to a six-membered ring requires the existence of four carbons in one plane. That cyclohexene oxide does indeed exist in the half-chair conformation has been demonstrated by Ottar (57) using electron diffraction measurements.

The reasoning which follows is equally applicable to both methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside and methyl 2,3-anhydro-4,6-O-benzylidene-α-D-mannopyranoside but for simplicity of exposition, discussion will be restricted to the former.

In the schematic representation of ring opening below,

the 4,6-O-benzylidene group is assumed to be present to hold the left hand portion of the system rigid but has been omitted in the interests of clarity.



Diequatorial Product Diaxial Product

In as far as the diaxial isomer is the one predominantly found, the diaxial transition state must be the more

stable. It is assumed that in the transition state, some return to the stable chair form has occurred and two factors contributing to the stability of the axial over the equatorial forms are now apparent. Firstly, the diaxial transition state has more nearly linear partial bonds than are to be found in the corresponding diequatorial state. Also, in the diaxial transition state, the attacking nucleophile is in the same plane as the epoxide ring, whereas in the diequatorial state, partial return to the chair conformation will impart some equatorial, and thus out of plane, character to the bonds.

Thus the above reaction scheme illustrates the formation of a 2-substituted sugar from the alloside and by means of an analogous representation, the opening of a mannoside ring to give a 3-substituted derivative can be explained.

In the present series of reactions, attack on the two anhydro sugars was carried out by the method of Prins et al (20,21), benzyl mercaptan being substituted for the methyl mercaptan of these earlier workers. Only one compound was isolated in the case of the alloside and similarly, only one was isolated in the reaction product from the mannoside. From the above considerations of preferential diaxial opening of epoxide rings, these two new compounds should be the 2- and 3-benzylthio sugars, respectively. However, it was decided to verify the positions of these thioether groups experimentally.

Maehly and Reichstein (58) have successfully reduced

methyl 4,6-O-benzylidene-2-deoxy-2-methylthio-α-D-idopyranoside to methyl 4,6-O-benzylidene-2-deoxy-α-D-gulopyranoside by reductive desulphurization with Raney nickel - a method which seemed well suited to the present purpose. The nickel catalyst was prepared in this laboratory according to Mozingo (59) and, following the procedure of Maehly and Reichstein, both methyl 4,6-O-benzylidene-2-deoxy-α-D-altropyranoside and methyl 4,6-O-benzylidene-3-deoxy-α-D-altropyranoside were obtained from the corresponding 2- and 3-benzylthio altrosides.

Standard reference compounds were prepared by the lithium aluminum hydride reduction of methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside and methyl 2,3-anhydro-4,6-O-benzylidene-α-D-mannopyranoside to the 2- and 3-deoxy altrosides, respectively (23). That these two deoxy sugars were indeed identical with the two obtained by reductive desulphurization of the benzylthio sugars was demonstrated by mixed melting points and infrared spectra.

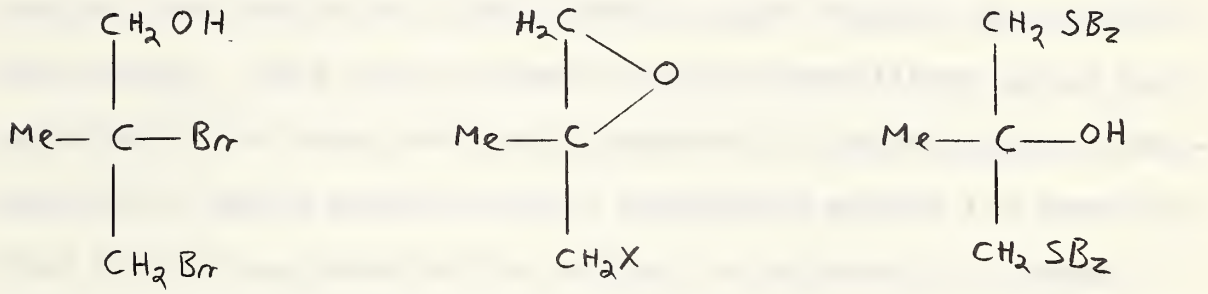
As a further check, a Keller-Killiani test (60) was performed on both reduced benzylthio sugars and a positive test was obtained only from that prepared from the alloside. While this test is not 100% specific for 2-deoxy sugars but is given by certain other substances also - notably some indole derivatives - a positive reaction under the present circumstances is certainly a very strong indication of the presence of a 2-deoxy sugar.

In a review on the cleavage of ethers, Burwell (61) devotes only one page to the subject of thioethers, but in tabular form compares the cleavage of anisole and thio-anisole. It is interesting to note that for the seven reducing agents listed, in only one instance does the yield of thiophenol compare favourably with that of phenol. This is in the case of the reduction by sodium in liquid ammonia when both are cleaved 100%. In fact, while lower dialkyl ethers are stable to this reducing agent, dialkyl sulphides are readily split by it. Burwell suggests the reason for this is that sulphur, unlike oxygen, can accommodate more than eight electrons in its outer shell and an electron or perhaps two can thus be added to the sulphur to give R_2S^- or R_2S^{--} which then dissociates.

Hartung (62), in his review on the hydrogenolysis of benzyl groups, is equally cursory in his treatment of the cleavage of benzyl sulphur bonds. The only method he discusses, albeit briefly, in this connection is that of sodium in liquid ammonia reduction. Birch (63) has reviewed the field of sodium in liquid ammonia reductions and includes several examples of the removal of the benzyl protecting group.

The debenzylation of S-benzylcysteine has been accomplished by the use of sodium in liquid ammonia (64) and this technique has been successfully applied in this laboratory to the preparation of mercapto indoles (34). A more recent

example of the same cleavage has been reported by Adams et al (65). These workers, in an attempt to synthesize anti-tubercular sulphur-containing compounds, treated 2,3-dibromo-2-methyl-propan-1-ol with benzyl mercaptan and obtained, they assume, through an epoxide intermediate, 1,3-dibenzylthio-2-methyl-propan-2-ol.



X = Br or SBz

Reduction of this dithioether with sodium in liquid ammonia gave the dithiol in 51% yield from the dibromide.

To date, no one appears to have applied the above method of reduction to the carbohydrates. Muskat (66) investigated the alkylation of carbohydrates in liquid ammonia and reports that all ordinary sugars, their acetylated and isopropylidene derivatives, are quite soluble in the medium. The solvent is without effect on them unless the anomeric carbon is free, in which case the amine is formed. He also - as later did Freudenberg (67) - treated diacetone glucose with theoretical

amounts of sodium and potassium to give salts which reacted readily with methyl and benzyl halides.

Application of sodium in liquid ammonia to the reduction of methyl 4,6-O-benzylidene-2-benzylthio-2-deoxy-α-D-altropyranoside gave a good yield of methyl 2-deoxy-2-mercapto-α-D-altropyranoside as a white solid which readily crystallized as needles from ethanol. It is interesting to note that, as well as cleaving the thioether to a free mercaptan, the sodium in liquid ammonia also removed the benzylidene group. This facile removal of the benzylidene group has apparently not been previously reported in carbohydrate chemistry but it would appear to be a convenient method for removing this protecting group while leaving the glycosidic linkage intact. Since 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (68) was shown in this work to be quite unaffected by sodium in liquid ammonia, this reductive cleavage may be specific for the benzylidene acetal.

On subjecting methyl 4,6-O-benzylidene-3-benzylthio-3-deoxy-α-D-altropyranoside to a similar reduction, a colourless syrup was isolated which readily solidified on trituration with water. It was recrystallized with some difficulty from ethanol and an infrared examination of the product showed two mercaptan peaks - one at 2555 cm^{-1} and the other at 2570 cm^{-1}. (Methyl 2-deoxy-2-mercapto-α-D-altropyranoside had a single mercaptan peak at 2575 cm^{-1}). Also a fairly strong

absorption band at 1665 cm^{-1} suggested the presence of a double bond. Attempts at purification by direct crystallization from a wide variety of solvents and solvent pairs were abortive. However, chromatography of the crude mercapto sugar on neutral alumina yielded bibenzyl in the initial fractions followed by a viscous colourless syrup which again readily solidified on trituration with water. Crystallization of this solid from ethyl propionate was slow but large prismatic crystals were produced. The infrared spectrum of these crystals showed only one mercaptan peak and gave no indication of unsaturation while an analysis agreed with the formulation of this substance as methyl 3-deoxy-3-mercapto-α-D-altropyranoside.

A chromatogram of the crude methyl 2-deoxy-2-mercapto-α-D-altropyranoside under the same conditions also yielded some bibenzyl in the initial fractions. Apparently this impurity is readily removed on recrystallization of the crude material from ethanol.

In an attempt to verify chemically the spectroscopic evidence of unsaturation in the reaction product obtained from the reduction of methyl 4,6-O-benzylidene-3-benzylthio-3-deoxy-α-D-altropyranoside, both bromine water and potassium permanganate tests were carried out. Both these reagents were instantaneously decolourized, but as a similar reaction was given by pure methyl 2-deoxy-2-mercapto-α-D-altropyranoside,

this can probably be attributed to the presence of the readily oxidizable mercaptan group. While tetranitro methane gave a positive yellow colour, the same result was obtained from unreduced methyl 4,6-O-benzylidene-3-benzylthio-3-deoxy-α-D-altropyranoside whose infrared spectrum shows no indication of unsaturation. Obviously some further work is necessary to explain the existence of the additional peak in the spectrum of the impure "methyl 3-deoxy-3-mercapto-α-D-altropyranoside".

While the simultaneous removal of the benzylidene group along with the reduction of the thioether to a mercaptan was advantageous in the present work, the possibility existed that, by using a limited amount of sodium, one might be reduced preferentially.

Since the reduction of methyl 4,6-O-benzylidene-2-benzylthio-2-deoxy-α-D-altropyranoside to methyl 2-deoxy-2-mercapto-α-D-altropyranoside had proceeded so smoothly, it was decided to use this as a model rather than the 3-isomer with its inherent complications.

Several different molar proportions of sodium were used. The first mole will be incorporated in the sodium salt of the free hydroxyl group on carbon 3 and a further two moles should then be sufficient to cleave the benzylthio ether. However, on examination of the reaction mixture obtained from methyl 4,6-O-benzylidene-2-benzylthio-2-deoxy-α-D-altropyranoside with three molar equivalents of sodium, only two products

were isolated - unchanged starting material and completely reduced methyl 2-deoxy-2-mercapto-α-D-altropyranoside. Similar results were obtained when the proportion of sodium was increased to four and five moles. It would thus appear that the preferential removal of one group is not possible by means of sodium in liquid ammonia.

Should it be desired to synthesize the 2- and 3-mercapto sugars with the protecting benzylidene group intact, by analogy with the work of Prey and Grundschober (11), one possible route would seem to be to treat the corresponding anhydro-alloside and anhydro-mannoside derivatives with hydrogen sulphide under increased pressure, though this was not suggested by these workers.

Hydrolysis of methyl 2-deoxy-2-mercapto-α-D-altropyranoside and the 3-mercapto isomer with N sulphuric acid gave yellow solids which charred on heating but would not melt. The broad indistinct bands of the infrared spectra showed the substances to be quite impure and afforded no information as to their structures. Neither they, nor the products obtained from attempts to prepare their acetyl, benzoyl or 3,5-dinitrobenzoyl derivatives, could be obtained in crystalline form. Since the methyl glycosides rather than the free reducing sugars were the ones immediately required for further study in this laboratory, further attempts at hydrolysis of these

glycosides were abandoned.

In view of the preceding successful synthesis of mercapto monosaccharides by an initial attack of sodium benzylmercaptide followed by a sodium in liquid ammonia reduction, it was decided to attempt to extend the scope of this method.

In 1922, Freudenberg and Brauns (69) reported that treatment of 1,2:5,6-di-O-isopropylidene-3-O-tosyl-α-D-glucofuranose with hydrazine for 20 hours at 140° C gave 3-deoxy-3-hydrazino-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose. However, more recent work (70) has shown this compound to be of the allose configuration. By analogy, it was thought that the benzylmercaptide ion might be induced to replace the tosyloxy group in a similar manner.

Several instances are recorded in the literature of the formation of thioethers by the attack of alkali metal mercaptides on primary tosyl groups, the first in the carbohydrate field being the work of Raymond (14). However, the tosyl group in question in the present work is an example of an isolated secondary group (36), which are well known to hydrolize only with difficulty, and then only by O-acyl fission without Walden inversion.

Reichstein (58,71) has shown that, like sodium hydroxide and methoxide, sodium methylmercaptide merely detosylates an isolated secondary tosyl group. Nevertheless, in view of

the high nucleophilicity of benzyl-mercaptide, it was decided to repeat Freudenberg's work using benzyl mercaptan in place of hydrazine in an attempt to synthesize 3-benzylthio-3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-allofuranose. However, here again, treatment of 1,2:5,6-di-O-isopropylidene-3-O-tosyl-α-D-glucofuranose with sodium benzylmercaptide resulted only in detosylation with retention of configuration about C_3.

EXPERIMENTAL

All melting points are uncorrected.

Methyl glucoside was prepared by the method of Helferich and Schafer (37). Dry methanol and powdered anhydrous glucose were refluxed for 72 hours in the presence of hydrochloric acid (0.25%) as a catalyst to give a 49% yield of methyl glucoside melting at 164-165° C.

Methyl 4,6-O-benzylidene-α-D-glucopyranoside

Basically, the procedure of Freudenberg, Toepffer and Anderson (38) was followed. Methyl glucoside and freshly distilled benzaldehyde were shaken with powdered anhydrous zinc chloride. However, to induce all solid material to dissolve, it was found necessary to extend the reaction time from three to twenty-four hours as recommended by Zervas (39) in the preparation of 4,6-O-benzylidene-α-D-glucopyranose. When the reaction mixture was poured into ice-cold water, the product solidified and was washed with more water. After several thorough washings with pentane to remove the excess benzaldehyde, the methyl 4,6-O-benzylidene-α-D-glucopyranoside was recrystallized from water from which it separated in long white needles in 40% yield. The melting point was found to be 161-162° C.

Purification of p-toluenesulphonyl chloride (tosyl chloride)

Practical grade tosyl chloride was dissolved in ether,

washed with sodium bicarbonate solution to remove any acid, and then with water until neutral. After being dried over sodium sulphate, the ether was removed by evaporation and the residual tosyl chloride was recrystallized from benzene.

Methyl 4,6-O-benzylidene-2,3-di-O-tosyl-α-D-glucopyranoside

A modification of the method of Ohle and Spencker (40) was employed. Methyl 4,6-O-benzylidene-α-D-glucopyranoside was dissolved in dry pyridine but only a 10% excess of tosyl chloride was added (36). To ensure complete esterification, the reaction time was extended from four days to a week. The original method of isolating the product by removal of the pyridine by distillation, was improved by Richtmyer and Hudson (41) who obtained the crystalline ditosyl compound by pouring the reaction mixture into ice-cold water. In the present work, this was further modified by the portionwise addition of a small quantity of water to hydrolize the excess tosyl chloride (36). A chloroform extract of the ester was washed with water to remove the excess pyridine and dried over sodium sulphate. Evaporation of the solvent left methyl 4,6-O-benzylidene-2,3-di-O-tosyl-α-D-glucopyranoside as a white solid. This was further purified by crystallization from methanol to give a 50% yield of the product melting at 147-148° C.

Methyl 4,6-O-benzylidene-2-O-tosyl-α-D-glucopyranoside

This was prepared by the method of Bolliger and Prins (42) involving an overnight treatment of methyl 4,6-O-benzylidene-α-D-glucopyranoside with a 10% excess of tosyl chloride in pyridine at room temperature. The product was isolated as outlined for the ditosyl ester above. Evaporation of the chloroform solvent left a viscous syrup which readily solidified on trituration with ether. Recyrstallization of a small quantity of this material from methanol yielded white crystals melting at 154-155°C. The yield of impure methyl 4,6-O-benzylidene-2-O-tosyl-α-D-glucopyranoside was 55%.

Methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside

Methyl 4,6-O-benzylidene-2,3-di-O-tosyl-α-D-glucopyranoside was dissolved in chloroform and left for a week at 0°C. in the presence of 2.7 N sodium methoxide (41). The solution was then diluted with water and extracted with chloroform. The chloroform extract, first washed and then dried over sodium sulphate, was freed from solvent. The remaining methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside was recrystallized from aqueous acetone from which it was deposited as long thin needles melting at 199-200°C. The yield of pure product was 93%.

Methyl 2,3-anhydro-4,6-O-benzylidene-α-D-mannopyranoside

As some difficulty was experienced in recrystallizing the methyl 4,6-O-benzylidene-2-O-tosyl-α-D-glucopyranoside, the

crude product was detosylated by refluxing for four hours in N sodium methoxide (49). The fine needles which separated on standing overnight were removed, washed with water and recrystallized from aqueous acetone. The yield of the anhydro sugar was 78% and the purified crystals melted at 146-147° C.

Benzyl Mercaptan

This was prepared according to Urquart's directions for lauryl mercaptan (72). Benzyl chloride and thiourea were heated in ethanol for 14 hours to give the S-benzylthiouronium hydrochloride. Addition of sodium hydroxide and further heating decomposed the salt to liberate the free benzyl mercaptan in 79% yield, boiling point 187° C/700 mm. All steps were carried out under an atmosphere of nitrogen.

Methyl 4,6-O-benzylidene-2-benzylthio-2-deoxy-α-D-altropyranoside

Sodium (2 g) was dissolved in methanol (40 ml) containing benzyl mercaptan (2.6 g, 0.022 mole). Methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside (5 g, 0.019 mole), (41,49) was added and the mixture then refluxed under nitrogen for two hours. The solution, left standing overnight at room temperature, deposited crystalline material which was removed and recrystallized from ethanol. The methanolic mother liquor was diluted with water and extracted with chloroform. The chloroform extract was washed with water until neutral and dried with sodium sulphate. Elimination of the solvent gave a further

quantity of crystalline material. Total yield of methyl 4,6-O-benzylidene-2-benzylthio-2-deoxy-α-D-altropyranoside was 7 g (95%). M.p., 136-137°C; $[\alpha]_{CHCl_3}^{D}$ at 22°, + 90.6° (C = 1.668). Anal. Calc. for $C_{21}H_{24}O_5S$: C, 64.93; H, 6.23; S, 8.25. Found: C, 64.97; H, 6.22; S, 8.30.

Methyl 4,6-O-benzylidene-3-benzylthio-3-deoxy-α-D-altropyranoside

Methyl 2,3-anhydro-4,6-O-benzylidene-α-D-mannopyranoside (49) was treated in a manner similar to that given the allo isomer with the exception that the reaction time was extended to 15 hours. Crystallization did not occur when the solution stood at room temperature overnight, therefore the reaction mixtures were diluted with water and extracted with chloroform. The chloroform solution was washed until neutral and dried with sodium sulphate. Removal of the solvent left a viscous syrup which solidified after trituration with ether. Recrystallization from methanol afforded colourless crystals. M.p. 105-106°C; yield, 88%; $[\alpha]_{CHCl_3}^{D}$ at 22°, + 54.9° (C = 1.436). Anal. Calc. for $C_{21}H_{24}O_5S$: C, 64.93; H, 6.23; S, 8.25. Found: C, 64.90; H, 6.44; S, 8.18.

Reductive Desulphurization of the above Thioethers

Methyl 4,6-O-benzylidene-2-benzylthio-2-deoxy-α-D-altropyranoside and methyl 4,6-O-benzylidene-3-benzylthio-3-deoxy-α-D-altropyranoside were desulphurized using Raney nickel

(59) according to the method employed by Maehly and Reichstein (58). A Keller-Kiliani test (60) was found to be positive for the product from the 2-benzylthio isomer and negative for the product from the 3-benzylthio isomer.

Preparation of Authentic 2-deoxy-and 3-deoxy-sugars

Both methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside (41,49) and methyl 2,3-anhydro-4,6-O-benzylidene-α-D-mannopyranoside (49) were reduced with lithium aluminum hydride according to the procedure described by Prins (23) to give respectively methyl 4,6-O-benzylidene-2-deoxy-α-D-altropyranoside and methyl 4,6-O-benzylidene-3-deoxy-α-D-altropyranoside. Comparison by means of mixed melting points and infrared spectra of these authentic deoxy-sugars with those obtained by the desulphurization of the benzylthio ethers as described above showed that the deoxy-sugar obtained from the desulphurization of the benzylthio ether prepared from the 2,3-anhydroalloside was in fact the 2-deoxyaltroside. The deoxy-sugar obtained from the desulphurization of the benzylthio ether prepared from the 2,3-anhydromannoside was definitely the 3-deoxyaltroside.

Methyl 2-deoxy-2-mercapto-α-D-altropyranoside

Finely powdered methyl 4,6-O-benzylidene-2-benzylthio-2-deoxy-α-D-altropyranoside (5 g) was added to liquid ammonia

(150 ml) in an Erlenmeyer flask cooled in dry ice. Small pieces of sodium metal were added to the solution, constantly stirred by a magnetic stirrer, until the blue colour persisted for 10 minutes. At the end of this time, ammonium chloride was added until the blue colour was discharged, whereupon the ammonia was allowed to evaporate, under a blanket of nitrogen to prevent oxidation of the mercaptan. The residue was extracted with chloroform (N_2) which, upon evaporation, left a colourless solid possessing a sweetish odor. Yield of crude product, 90%; m.p., 140-145°C. Recrystallization from ethanol, in which the compound was found to be quite soluble, yielded small, colourless needles, m.p. 145-146°C; $[\alpha]^{D}_{CHCl_3}$, + 95.2° (C = 0.9352). Anal. Calc. for $C_7H_{14}O_5S$: C, 39.99; N, 6.71; S, 15.25. Found C, 39.95; H, 6.71; S, 15.14.

Methyl 3-deoxy-3-mercapto-α-D-altropyranoside

Finely powdered methyl 4,6-O-benzylidene-3-benzylthio-3-deoxy-α-D-altropyranoside was subjected to a sodium in liquid ammonia reduction under the same conditions as outlined above for the 2-isomer. On removal of the solvent from the chloroform extract, a colourless viscous syrup remained which solidified on trituration with water. A solution of this material in a benzene-methanol mixture (5:1) was passed through a column of neutral alumina* prepared in benzene. The initial fractions contained bibenzyl and were discarded. Subsequent

* Woelm Aluminum Oxide. Neutral, activity grade 1. Distributed by Alupharm Chemicals, P.O. Box 755, New Orleans, La.

fractions yielded a colourless viscous syrup which solidified when triturated with water.

Several recrystallizations from ethyl propionate gave pure methyl 3-deoxy-3-mercapto-α-D-altropyranoside as large prismatic crystals. M.p. 85-85°C; $[\alpha]_{H_2O}^{D}$, + 68.6° (C = 1.428). Anal. Calc. for $C_7H_{14}O_5S$: C, 39.99; H, 6.71; S, 15.25. Found: C, 40.08; H, 6.80; S, 15.44

Attempted Hydrolysis of the Methyl 2-and 3-mercaptoaltrosides

Methyl 2-deoxy-2-mercapto-α-D-altropyranoside was dissolved in N sulphuric acid and heated in a boiling water bath for four hours under nitrogen. The brown solution was neutralized with barium carbonate and the precipitated barium sulphate was removed. Treatment with charcoal under a nitrogen atmosphere gave a yellow solution. Removal of the water under vacuum left a yellow solid which could not be purified by recrystallization, nor could satisfactory products be obtained in attempts to prepare its acetyl, benzoyl or 3,5-dinitrobenzoyl derivatives. The yellow aqueous solution reacted with Fehling's solution to give a yellow precipitate.

An identical procedure was applied to methyl 3-deoxy-3-mercapto-α-D-altropyranoside but with the same unsuccessful results.

1,2:5,6-Di-O-isopropylidene-α-D-glucofuranose

The procedure of Grunenberg, Bredt and Freudenberg (68)

was followed. Finely powdered glucose was shaken at room temperature for two hours in dry acetone and in the presence of a catalyst consisting of one part phosphorous pentoxide, two parts phosphoric acid and six parts anhydrous zinc chloride. After standing overnight to allow the reaction to go to completion, the mixture was made alkaline with an aqueous suspension of sodium carbonate and the precipitated zinc carbonate was separated. Most of the acetone was removed under vacuum and the remaining aqueous residue was extracted with benzene. Evaporation of the solvent left diacetone glucose in a high state of purity and when crystallized from ligroin, it melted at 109-110°C. The yield was 75%.

1,2:5,6-Di-O-isopropylidene-3-O-tosyl-α-D-glucofuranose

This preparation was based on the work of Freudenberg and Ivers (73). 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose and a 10% excess of tosyl chloride were dissolved in dry pyridine and left for 14 hours at 30°C. At the end of this time, small quantities of water were added over a period of an hour, as in previous tosylations, to destroy excess tosyl chloride. The pyridine solution was then poured into ice-cold water whereupon the ester solidified. Crystallization from methanol gave an 85% yield of 1,2:5,6-di-O-isopropylidene-3-O-tosyl-α-D-glucofuranose melting at 120-121°C.

Attempted Synthesis of 3-benzylthio-3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-allofuranose

To a solution of 2.6 g of benzyl mercaptan in 50 ml of methanol was added 2 g of sodium metal. After subsequent addition of 5 g of 1,2: 5,6-di-O-isopropylidene-3-O-tosyl-α-D-glucofuranose (73) the mixture was refluxed overnight under a blanket of nitrogen. A chloroform extract of the cooled reaction mixture, first diluted with water, was washed with water until it was neutral, and then dried with sodium sulphate. Removal of the chloroform left a colourless solid which, when crystallized from ligroin, proved to be 1,2: 5,6-di-O-isopropylidene-α-D-glucofuranose. Even more extreme conditions, using dimethylformamide as solvent and a temperature of 130-135°C for 20 hours, failed to give any product other than the detosylated diacetone glucose.

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